Atty. Docket No: Z9996.488/PQ01-A

In re patent application of

Serrero, Ginette

Serial No. 08/991,862

Filed: December 16, 1997

For: 88 KDA TUMORIGENIC GROWTH FACTOR AND ANTAGONISTS

## STATEMENT TO SUPPORT FILING AND SUBMISSION IN ACCORDANCE WITH 37 C.F.R. §§ 1.821-1.825

Assistant Commissioner for Patents Washington, D.C. 20231
Box SEQUENCE

Sir:

In connection with a Sequence Listing submitted concurrently herewith, the undersigned hereby states that:

- the submission, filed herewith in accordance with 37
   C.F.R. § 1.821(g), does not include new matter;
- 2. the content of the attached paper copy and the attached computer readable copy of the Sequence Listing, submitted in accordance with 37 C.F.R. § 1.821(c) and (e), respectively, are the same; and
- 3. all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United

States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Respectfully submitted,

James A. Coburn

Date

HARBOR CONSULTING

Intellectual Property Services 1500A Lafayette Road Suite 262 Portsmouth, N.H. 800-318-3021

## SEQUENCE LISTING

<110> Serrero, Ginette	
<120> 88 KDA TUMORIGENIC GROWTH FACTOR AND ANTAGONISTS	
<130> Z9996.488/P001-A	
<140> 08/991,862 <141> 1997-12-16	
<150> 08/863,862 <151> 1997-05-23	
<160> 17	
<170> PatentIn Ver. 2.0	
<210> 1 <211> 2137 <212> DNA <213> Mouse epithelin/granulin	
<220> <221> CDS <222> (23)(1789) <223> The sequence is identical to that of the published mouse granulin except for one nucleotide (T instead of G) at position 1071 of GP88 cDNA (position 1056 of mouse granulin).	
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gcg gca ggg ctg gta gcc gga aca cag tgt cca gat ggg cag ttc tgc Ala Ala Gly Leu Val Ala Gly Thr Gln Cys Pro Asp Gly Gln Phe Cys 15 20 25	100
cct gtt gcc tgc tgc ctt gac cag gga gga gcc aac tac agc tgc tgt Pro Val Ala Cys Cys Leu Asp Gln Gly Gly Ala Asn Tyr Ser Cys Cys 30 35 40	148
aac cct ctt ctg gac aca tgg cct aga ata acg agc cat cat cta gat Asn Pro Leu Leu Asp Thr Trp Pro Arg Ile Thr Ser His His Leu Asp 45 50 55	196
ggc tcc tgc cag acc cat ggc cac tgt cct gct ggc tat tct tgt ctt Gly Ser Cys Gln Thr His Gly His Cys Pro Ala Gly Tyr Ser Cys Leu 60 65 70	244
ctc act gtg tct ggg act tcc agc tgc tgc ccg ttc tct aag ggt gtg Leu Thr Val Ser Gly Thr Ser Ser Cys Cys Pro Phe Ser Lys Gly Val 75 80 85 90	292

340

tct tgt ggt gat ggc tac cac tgc tgc ccc cag ggc ttc cac tgt agt Ser Cys Gly Asp Gly Tyr His Cys Cys Pro Gln Gly Phe His Cys Ser 95 100 105

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-							_	_				ccc Pro				388
~	_	-			-	_		-	-		-	tct Ser 135				436
												atg Met				484
												ggg Gly				532
_		~			_	~	_			-		acc Thr				580
	_				_		_			_		gtg Val		_		628
												ccc Pro 215				676
	_	_						_			_	tgt Cys				724
	Āla		_	_		Āsp		_		-	-	ccc Pro	_	_		772
										Ser		aac Asn				820
_		_		Lys	_				Pro		_			_	tgc Cys	868
_	_		Val	-			-	ıĞİy			_	_	Arg		aac Asn	916
		Ala			_	_	Pro		-	_	_	ı Val	_	-	gac S Asp	964
	) His					s Pro					о Суз				aaa Lys 330	1012
					Gly				-	L Gly			_		g gtc s Val	1060

			ctc Leu 350		_		-		-				_			1108
	-	-	gac Asp				-							_		1156
			Gly				_	_								1204
_		~	aac Asn	_		_	_						_	_	_	1252
			tgt Cys													1300
			cgc Arg 430	_			_							_	_	1348
-	_		acc Thr	-	-		_				_	_		-		1396
			tgg Trp													1444
	Arg										Cys				gcg Ala 490	1492
		_		-	Āsp	-	-			Gln					ctg Leu	1540
				Lys					Glu					His	ttc Phe	1588
			Asn					Lys					Val		gcc Ala	1636
Cys	540	Pro	) Tyr	Leu	Lys	545	v Val	Cys	Cys	Arg	550	Gly	Arg	g His	tgt Cys	1684
Cys 555	Pro	Gly	/ Gly	, Ph∈	9 His 560	s Cys	s Ser	Ala	a Arç	565	y Thr	Lys	су Су	s Lei	y cga 1 Arg 570	1732
					g Trp					Arg					a aga o Arg	1780

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Asp Gln Gly Gly Ala Asn Tyr Ser Cys Cys Asn Pro Leu Leu Asp Thr 40

Trp Pro Arg Ile Thr Ser His His Leu Asp Gly Ser Cys Gln Thr His

Gly His Cys Pro Ala Gly Tyr Ser Cys Leu Leu Thr Val Ser Gly Thr

Ser Ser Cys Cys Pro Phe Ser Lys Gly Val Ser Cys Gly Asp Gly Tyr

His Cys Cys Pro Gln Gly Phe His Cys Ser Ala Asp Gly Lys Ser Cys

Phe Gln Met Ser Asp Asn Pro Leu Gly Ala Val Gln Cys Pro Gly Ser 115 120

Gln Phe Glu Cys Pro Asp Ser Ala Thr Cys Cys Ile Met Val Asp Gly 135

Ser Trp Gly Cys Cys Pro Met Pro Gln Ala Ser Cys Cys Glu Asp Arg 145 150 155

Val His Cys Cys Pro His Gly Ala Ser Cys Asp Leu Val His Thr Arg

Cys Val Ser Pro Thr Gly Thr His Thr Leu Leu Lys Lys Phe Pro Ala

Gln Lys Thr Asn Ser Ala Val Ser Leu Pro Phe Ser Val Val Cys Pro 200

Asp Ala Lys Thr Glacys Pro Asp Asp Ser Thr Cys Cys Glac Leu Pro 210 215 220

Thr Gly Lys Tyr Gly Cys Cys Pro Met Pro Asn Ala Ile Cys Cys Ser 225 230 235 240

Asp His Leu His Cys Cys Pro Gln Asp Thr Val Cys Asp Leu Ile Gln 245 250 255

Ser Lys Cys Leu Ser Lys Asn Tyr Thr Thr Asp Leu Leu Thr Lys Leu 260 270

Pro Gly Tyr Pro Val Lys Glu Val Lys Cys Asp Met Glu Val Ser Cys 275 280 285

Pro Glu Gly Tyr Thr Cys Cys Arg Leu Asn Thr Gly Ala Trp Gly Cys 290 295 300

Cys Pro Phe Ala Lys Ala Val Cys Cys Asp Asp His Ile His Cys Cys 305 310 315 320

Pro Ala Gly Phe Gln Cys His Thr Glu Lys Gly Thr Cys Glu Met Gly
325 330 335

Ile Leu Gln Val Gly Trp Met Lys Lys Val Ile Ala Pro Leu Arg Leu 340 345 350

Pro Asp Pro Gln Ile Leu Lys Ser Asp Thr Pro Cys Asp Asp Phe Thr 355 360 365

Arg Cys Pro Thr Asn Asn Thr Cys Cys Lys Leu Asn Ser Gly Asp Trp 370 375 380

Gly Cys Cys Pro Ile Pro Glu Ala Val Cys Cys Ser Asp Asn Gln His 385 390 395 400

Cys Cys Pro Gln Gly Phe Thr Cys Leu Ala Gln Gly Tyr Cys Gln Lys 405 410 415

Gly Asp Thr Met Val Ala Gly Leu Glu Lys Ile Pro Ala Arg Gln Thr 420 425 430

Thr Pro Leu Gln Ile Gly Asp Ile Gly Cys Asp Gln His Thr Ser Cys
435
440
445

Pro Val Gly Gln Thr Cys Cys Pro Ser Leu Lys Gly Ser Trp Ala Cys 450 460

Cys Gln Leu Pro His Ala Val Cys Cys Glu Asp Arg Gln His Cys Cys 465 470 475 480

Pro Ala Gly Tyr Thr Cys Asn Val Lys Ala Arg Thr Cys Glu Lys Asp 485 490 495

Val Asp Phe Ile Gln Pro Pro Val Leu Leu Thr Leu Gly Pro Lys Val 500 505 510

Gly Asn Val Glu Cys Gly Glu Gly His Phe Cys His Asp Asn Gln Thr 515 520 525

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Cys Cys Lys Asp Ser Ala Gly Val Trp Ala Cys Cys Pro Tyr Leu Lys
                        535
                                             540
Gly Val Cys Cys Arg Asp Gly Arg His Cys Cys Pro Gly Gly Phe His
545
                    550
Cys Ser Ala Arg Gly Thr Lys Cys Leu Arg Lys Lys Ile Pro Arg Trp
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Asp Met Phe Leu Arg Asp Pro Val Pro Arg Pro Leu Leu
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<212> PRT
<213> mouse granulin
<220>
<221> PEPTIDE
<222> (1)...(19)
<223> Internal peptide of mouse GP88 used to raise the
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 <222> (1)..(12)
 <223> Internal peptide of mouse GP88 used to raise the
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 Pro Asp Ala Lys Thr Gln Cys Pro Asp Asp Ser Thr
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 <212> PRT
 <213> mouse granulin
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 <221> PEPTIDE
 <222> (1)..(14)
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<223> Internal peptide of mouse GP88 used to raise the antisera against the GP88 used in the

immunoaffinity step.

<213> mammalian

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<213> Human granulin
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<221> PEPTIDE
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<223> Internal peptide of human GP88 used to develop
      neutralizing anti-human GP88 monoclonal antibody.
Glu Lys Ala Pro Ala His Leu Ser Leu Pro Asp Pro Gln Ala Leu Lys
                                      10
Arg Asp Val
<210> 7
<211> 14
<212> PRT
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<221> PEPTIDE
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                   5
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 <211> 24
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 <220>
 <221> primer
 <222> (1)..(24)
 <223> Internal peptide of CMV promoter used as PCR
       primer.
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 <210> 9
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 <212> DNA
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<221> primer
<222> (1)..(27)
<223> GP88 cDNA start codon used as oligonucleotide PCR
      primer.
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                                                                    27
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<211> 27
<212> DNA
<213> mammalian
<220>
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<222> (1)..(27)
<223> Antisense primer oligonucleotide primer
                                                                    27
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                                                                     25
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<220> <221> CDS <222> (13)(1791) <223> Nucleotide sequence of human granulin/epithelin precursor (human GP88). Human Granulin Genebank M75161.	
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ctg gtg gct gga acg cgg tgc cca gat ggt cag ttc tgc cct gtg gcc Leu Val Ala Gly Thr Arg Cys Pro Asp Gly Gln Phe Cys Pro Val Ala 15 20 25	99
tgc tgc ctg gac ccc gga gga gcc agc tac agc tgc tgc cgt ccc ctt Cys Cys Leu Asp Pro Gly Gly Ala Ser Tyr Ser Cys Cys Arg Pro Leu 30 35 40 45	147
ctg gac aaa tgg ccc aca aca ctg agc agg cat ctg ggt ggc ccc tgc Leu Asp Lys Trp Pro Thr Thr Leu Ser Arg His Leu Gly Gly Pro Cys 50 55 60	195

											tgc Cys					243
											gcc Ala					291
											tgc Cys 105					339
											gtg Val					387
											tcc Ser					435
											ccc Pro					483
						_	_				gcc Ala					531
			-	_			Pro	_			cac His 185		_	_		579
			-	_					_		gcc Ala	_				627
_	_	_	_	-	-				_	Pro	gat Asp				-	675
				Ser	Gly	Lys	Tyr	Gly	Cys	Cys	cca Pro	Met		Asn	-	723
			Ser					Cys			caa Gln		Thr			771
		Ile					Leu					Ala			gac Asp	819
cto Leu 270	ı Lev	act Thr	aaç Lys	r ctg Leu	cct Pro 275	Ala	g cac His	aca Thr	gtg Val	g ggc . Gly 280	/ Asp	gtç Val	, aaa . Lys	tgt Cys	gac Asp 285	867
					Pro					Cys					g tcg n Ser )	. 915

,				4				•			×		4			
				tgc Cys												963
				tgt Cys												1011
				ggg Gly												1059
				ctg Leu												1107
				agc Ser 370												1155
				tgg Trp												1203
				cac His												1251
				cga Arg			Glu								atg Met	1299
				ggt Gly							Asp				gac Asp 445	1347
										Cys					ggt Gly	1395
				Cys					His					Glu	g gat 1 Asp	1443
			Cys					Tyr					Lys		cga Arg	1491
		Glu					L Ser					Thr			g gcc ı Ala	1539
	Ser					/ Val					ı Cys				a•cac y His 525	1587
			_		Gli		_		_	g Ásı			_		c tgg y Trp O	1635

Ala Cys Cys Pro Tyr Ala Gln Gly Val Cys Cys Ala Asp Arg Arg His 545 550 555
tgc tgt cct gct ggc ttc cgc tgc gca cgc agg ggt acc aag tgt ttg 1731 Cys Cys Pro Ala Gly Phe Arg Cys Ala Arg Arg Gly Thr Lys Cys Leu 560 565 570
cgc agg gag gcc ccg cgc tgg gac gcc cct ttg agg gac cca gcc ttg 1779 Arg Arg Glu Ala Pro Arg Trp Asp Ala Pro Leu Arg Asp Pro Ala Leu 575 580 585
aga cag ctg ctg tgagggacag tactgaagac tctgcagccc tcgggacccc 1831 Arg Gln Leu Leu 590
acteggaggg tgccctctgc tcaggcctcc ctagcacctc cccctaacca aattctccct 1891
ggaccccatt ctgagctccc catcaccatg ggaggtgggg cctcaatcta aggcccttcc 1951
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Met Trp Thr Leu Val Ser Trp Val Ala Leu Thr Ala Gly Leu Val Ala  1 5 10 15  Gly Thr Arg Cys Pro Asp Gly Gln Phe Cys Pro Val Ala Cys Cys Leu 20 25 30  Asp Pro Gly Gly Ala Ser Tyr Ser Cys Cys Arg Pro Leu Leu Asp Lys
Met Trp Thr Leu Val Ser Trp Val Ala Leu Thr Ala Gly Leu Val Ala  1
Met Trp Thr Leu Val Ser Trp Val Ala Leu Thr Ala Gly Leu Val Ala 1 15  Gly Thr Arg Cys Pro Asp Gly Gln Phe Cys Pro Val Ala Cys Cys Leu 20  Asp Pro Gly Gly Ala Ser Tyr Ser Cys Cys Arg Pro Leu Leu Asp Lys 45  Trp Pro Thr Thr Leu Ser Arg His Leu Gly Gly Pro Cys Gln Val Asp 50  Ala His Cys Ser Ala Gly His Ser Cys Ile Phe Thr Val Ser Gly Thr
Met Trp Thr Leu Val Ser Trp Val Ala Leu Thr Ala Gly Leu Val Ala 1 10 15    Gly Thr Arg Cys Pro Asp Gly Gln Phe Cys Pro Val Ala Cys Cys Leu 20    Asp Pro Gly Gly Ala Ser Tyr Ser Cys Cys Arg Pro Leu Leu Asp Lys 40    Trp Pro Thr Thr Leu Ser Arg His Leu Gly Gly Pro Cys Gln Val Asp 50    Ala His Cys Ser Ala Gly His Ser Cys Ile Phe Thr Val Ser Gly Thr 65    Ser Ser Cys Cys Pro Phe Pro Glu Ala Val Ala Cys Gly Asp Gly His
Met Trp Thr Leu Val Ser Trp Val Ala Leu Thr Ala Gly Leu Val Ala 15  Gly Thr Arg Cys Pro Asp Gly Gln Phe Cys Pro Val Ala Cys Cys Leu 20  Asp Pro Gly Gly Ala Ser Tyr Ser Cys Cys Arg Pro Leu Leu Asp Lys 45  Trp Pro Thr Thr Leu Ser Arg His Leu Gly Gly Pro Cys Gln Val Asp 50  Ala His Cys Ser Ala Gly His Ser Cys Ile Phe Thr Val Ser Gly Thr 65  Ser Ser Cys Cys Pro Phe Pro Glu Ala Val Ala Cys Gly Asp Gly His 90  His Cys Cys Pro Arg Gly Phe His Cys Ser Ala Asp Gly Arg Ser Cys

Gly Ser Trp Gly Cys s Pro Met Pro Gln Ala Ser Cys Cys lu Asp 145 150 150 160

Arg Val His Cys Cys Pro His Gly Ala Phe Cys Asp Leu Val His Thr 165 170 175

Arg Cys Ile Thr Pro Thr Gly Thr His Pro Leu Ala Lys Lys Leu Pro 180 185

Ala Gln Arg Thr Asn Arg Ala Val Ala Leu Ser Ser Ser Val Met Cys 195 200 205

Pro Asp Ala Arg Ser Arg Cys Pro Asp Gly Ser Thr Cys Cys Glu Leu 210 215 220

Pro Ser Gly Lys Tyr Gly Cys Cys Pro Met Pro Asn Ala Thr Cys Cys 225 230 235

Ser Asp His Leu His Cys Cys Pro Gln Asp Thr Val Cys Asp Leu Ile 245 250 255 ~

Gln Ser Lys Cys Leu Ser Lys Glu Asn Ala Thr Thr Asp Leu Leu Thr 260 265 270

Lys Leu Pro Ala His Thr Val Gly Asp Val Lys Cys Asp Met Glu Val 275 280 285

Ser Cys Pro Asp Gly Tyr Thr Cys Cys Arg Leu Gln Ser Gly Ala Trp 290 295 300

Gly Cys Cys Pro Phe Thr Gln Ala Val Cys Cys Glu Asp His Ile His 305 310 315 320

Cys Cys Pro Ala Gly Phe Thr Cys Asp Thr Gln Lys Gly Thr Cys Glu 325 330 335

Gln Gly Pro His Gln Val Pro Trp Met Glu Lys Ala Pro Ala His Leu 340 345 350

Ser Leu Pro Asp Pro Gln Ala Leu Lys Arg Asp Val Pro Cys Asp Asn 360 365

Val Ser Ser Cys Pro Ser Ser Asp Thr Cys Cys Gln Leu Thr Ser Gly 370 375 380

Glu Trp Gly Cys Cys Pro Ile Pro Glu Ala Val Cys Cys Ser Asp His 385 390 395 400

Gln His Cys Cys Pro Gln Arg Tyr Thr Cys Val Ala Glu Gly Gln Cys 405 410 415

Gln Arg Gly Ser Glu Ile Val Ala Gly Leu Glu Lys Met Pro Ala Arg 420 425 430

Arg Gly Ser Leu Ser His Pro Arg Asp Ile Gly Cys Asp Gln His Thr 435 440 445

Ser Cys Pro Val Gly Gly Thr Cys Cys Pro Ser Gln Gly Gly Ser Trp 450 460

Ala Cys Cys Gln Leu ro His Ala Val Cys Cys Glu Asp Arg sln His 465 470 475 480

Cys Cys Pro Ala Gly Tyr Thr Cys Asn Val Lys Ala Arg Ser Cys Glu 485 490 495

Lys Glu Val Val Ser Ala Gln Pro Ala Thr Phe Leu Ala Arg Ser Pro 500 505 510

His Val Gly Val Lys Asp Val Glu Cys Gly Glu Gly His Phe Cys His 515 520 525

Asp Asn Gln Thr Cys Cys Arg Asp Asn Arg Gln Gly Trp Ala Cys Cys 530 540

Pro Tyr Ala Gln Gly Val Cys Cys Ala Asp Arg Arg His Cys Cys Pro 545 550 555 560

Ala Gly Phe Arg Cys Ala Arg Arg Gly Thr Lys Cys Leu Arg Arg Glu 565 570 575

Ala Pro Arg Trp Asp Ala Pro Leu Arg Asp Pro Ala Leu Arg Gln Leu 580 585 590

Leu